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## Recanalization Therapies in Acute Ischemic Stroke Patients: Impact of Prior Treatment With Novel Oral Anticoagulants on Bleeding Complications and Outcome

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**Abstract:** **BACKGROUND** We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in patients with ischemic stroke on non-vitamin K antagonist oral anticoagulants (NOACs, last intake <48 hours) in comparison with patients (1) taking vitamin K antagonists (VKAs) or (2) without previous anticoagulation (no-OAC). **METHODS AND RESULTS** This is a multicenter cohort pilot study. Primary outcome measures were (1) occurrence of intracranial hemorrhage (ICH) in 3 categories: any ICH (ICHany), symptomatic ICH according to the criteria of the European Cooperative Acute Stroke Study II (ECASS-II) (sICHECASS-II) and the National Institute of Neurological Disorders and Stroke (NINDS) thrombolysis trial (sICHNINDS); and (2) death (at 3 months). Cohorts were compared by using propensity score matching. Our NOAC cohort comprised 78 patients treated with IVT/IAT and the comparison groups of 441 VKA patients and 8938 no-OAC patients. The median time from last NOAC intake to IVT/IAT was 13 hours (interquartile range, 8-22 hours). In VKA patients, median pre-IVT/IAT international normalized ratio was 1.3 (interquartile range, 1.1-1.6). ICHany was observed in 18.4% NOAC patients versus 26.8% in VKA patients and 17.4% in no-OAC patients. sICHECASS-II and sICHNINDS occurred in 2.6%/3.9% NOAC patients, in comparison with 6.5%/9.3% of VKA patients and 5.0%/7.2% of no-OAC patients, respectively. At 3 months, 23.0% of NOAC patients in comparison with 26.9% of VKA patients and 13.9% of no-OAC patients had died. Propensity score matching revealed no statistically significant differences. **CONCLUSIONS** IVT/IAT in selected patients with ischemic stroke under NOAC treatment has a safety profile similar to both IVT/IAT in patients on subtherapeutic VKA treatment or in those without previous anticoagulation. However, further prospective studies are needed, including the impact of specific coagulation tests.

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**Title: Impact of prior treatment with novel oral anticoagulants on bleeding complications and outcome in acute stroke patients treated with recanalization therapies**

**Short title: Recanalization in stroke patients on NOAC**

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## Abstract

### Background:

We explored the safety of intravenous thrombolysis (IVT) or intra-arterial treatment (IAT) in ischemic stroke patients on novel oral anticoagulants (NOAC, last intake <48hours) compared to patients (i) taking vitamin K-antagonists (VKA) or (ii) without prior anticoagulation (no-oAC).

### Methods and Results:

Multicenter cohort pilot study. Primary outcome measures were (i) occurrence of ICH in three categories - any intracranial hemorrhage (ICH<sub>any</sub>), symptomatic ICH according to the criteria of the ECASS-II (sICH<sub>ECASS-II</sub>) and the NINDS thrombolysis trial (sICH<sub>NINDS</sub>); and (ii) death (at 3 months). Secondary outcomes included favorable 3-months outcome (modified Rankin Scale score 0-2). Cohorts were compared by using propensity score matching. Our NOAC cohort comprised of 78 patients treated with IVT/IAT and the comparison groups of 441 VKA-patients and 8938 no-oAC patients. The median time from last NOAC intake to IVT/IAT was 13 hours (IQR 8-22h). In VKA-patients median pre-IVT/IAT INR was 1.3 (IQR 1.1-1.6). ICH<sub>any</sub> was observed in 18.4% NOAC patients versus 26.8% VKA patients and 17.4% no-oAC patients. sICH<sub>ECASS-II</sub> and sICH<sub>NINDS</sub> occurred in 2.6%/3.9 % NOAC patients, compared to 6.5%/9.3% VKA patients and 5.0%/7.2% no-oAc patients, respectively. At 3 months, 23.0% NOAC patients compared to 26.9% VKA patients and 13.9% no-oAC patients had died. Propensity score matching revealed no statistical significant differences.

### Conclusion:

IVT/IAT in selected patients with ischemic stroke under NOAC treatment has a safety profile similar to both, IVT/IAT in patients on subtherapeutic VKA-treatment or in those without prior anticoagulation. However, further prospective studies are needed, including the impact of specific coagulation tests.

Key words: intravenous thrombolysis, novel oral anticoagulants, vitamin K antagonists, ischemic stroke, intra-arterial treatment, endovascular treatment intracranial hemorrhage

## Introduction

Atrial fibrillation is one of the major risk factors for ischemic stroke<sup>1</sup>. Novel oral anticoagulants (NOAC) are at least as effective as Vitamin K-antagonists (VKA) in preventing ischemic stroke in patients with atrial fibrillation, with a better safety profile, especially for intracranial bleeding<sup>2-4</sup>. VKA act as indirect anticoagulants which lower the functional level of different vitamin-K dependent coagulation factors. In contrast, NOAC directly target selected players in the coagulation cascade as the direct thrombin inhibitor dabigatran or the factor-Xa inhibitors apixaban, rivaroxaban and edoxaban<sup>2,5</sup>. Therefore, onset of the anticoagulatory effect of NOACs is sudden (peak levels between 2 and 5 hours after intake). Anticoagulation lasts only for several hours to a few days while treatment with VKA results in a sustained, long lasting inhibition of the coagulation cascade<sup>6</sup>.

1-2% of all individuals have atrial fibrillation, a proportion that will increase as populations age and diagnostic procedures improve. Despite the best medical treatment with VKA or NOAC 1.11-3.24% of patients with atrial fibrillation will have a new ischemic stroke annually<sup>2</sup>. Furthermore, also patients taking VKA or NOAC for indications other than atrial fibrillation can get an acute stroke. Many of these patients will be evaluated at emergency rooms for eligibility for acute recanalization therapies. For patients with ischemic stroke being treated with VKA, there are both guidelines<sup>7</sup> and register-based observational data<sup>8, 9</sup> indicating that the use of intravenous thrombolysis (IVT) or intra-arterial-treatment (IAT) can be safe under certain conditions.

However, it remains uncertain how patients developing acute ischemic stroke while taking NOAC should be treated. Current guidelines consider IVT contraindicated, and mention the cautious use of IAT<sup>7</sup>. Currently, millions of patients with atrial fibrillation worldwide are treated with NOAC, a number that will continue to increase. Withholding acute recanalization therapies from all patients with acute stroke and a last intake of NOAC within 48 hours would deny a substantial number of acute stroke patients an effective treatment.

Nevertheless, theoretical approaches to guide the use of IVT or IAT in stroke patients taking NOAC have been published<sup>10-13</sup>. Furthermore, a few case reports on the use of IVT in patients taking dabigatran<sup>14-18</sup>, rivaroxaban<sup>19-22</sup> or apixaban<sup>23</sup> or IAT while taking dabigatran<sup>24</sup> reported favorable clinical outcomes. Conversely, one patient with acute ischemic stroke under dabigatran had a fatal intracranial hemorrhage (ICH) associated with IVT<sup>25</sup>. Thus, currently, there is a lack of systematic outcome and safety data in patients with acute ischemic stroke under NOAC treatment at the time of IVT or IAT. Standardized data in large cohorts including any comparison group are not available. As a pilot project, we therefore

investigated the safety of IVT and IAT for acute ischemic stroke in patients taking NOAC. Findings in NOAC-patients were compared with (i) those taking VKA and (ii) patients without anticoagulation (no-oAC) prior to IVT/IAT in a large multicenter observational cohort study.

## Material and Methods

### Study design and study population

As a joint initiative of 25 European and Japanese stroke centers, we performed an observational collaborative cohort study to investigate: (i) the incidence of intracranial hemorrhages (ICH); and (ii) functional outcome of patients with acute ischemic stroke occurring under NOAC who were treated with IVT or IAT or both (i.e., bridging). IAT included intra-arterial thrombolysis, mechanical revascularization, or both. We introduced two comparisons groups: First, stroke patients with IVT and/or IAT under VKA and, second, patients without anticoagulation at the time of IVT/IAT.

All participating centers applied IVT and IAT according to well-established criteria and guidelines<sup>7, 26</sup> with the exception that in selected patients NOAC treatment was not considered an absolute exclusion criterion.

Each center reported on all NOAC patients treated with IVT/IAT during the period for which they had prospectively recorded data on consecutive patients treated with IVT/IAT in local registries or lists since approval of the first NOAC for stroke prevention in atrial fibrillation in their country up to December 31<sup>st</sup> 2014. Selected centers also provided information on all stroke patients treated with IVT/IAT (i) under VKA and (ii) those without prior anticoagulation (no-oAC) based on local registries. For each contributing center, the number of patients, recruitment periods and type of data source (i.e. register versus patient lists) are summarized in online supplemental Table 1.

### Data collection

Data for all patients were collected using a standardized form with predefined variables, following an approach utilized in prior research<sup>27-29</sup>. Local study investigators retrospectively completed the forms systematically using data from (i) prospectively ascertained in-hospital thrombolysis or stroke-registries or (ii) from patients' records and charts in case patients were selected and identified by local patients lists about consecutive IVT/IAT. Completed forms from all centers were sent to the coordinating center in Basel, where analyses of pooled data were performed.

### Baseline data

The following variables were collected from the centers' databases, registries or patients' records as previously defined<sup>27-29</sup>: age, sex, stroke severity as assessed by the National



Institutes of Health Stroke Scale (NIHSS) score prior to IVT/IAT and after 24 hours, international normalized range (INR), presence or absence of main intracranial arteries occlusion (assessed by CTA or MRA), blood pressure, time-to-treatment and etiology according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. A descriptive summary is given in Table 1. In addition, the following vascular risk factors were collected according to predefined criteria<sup>27</sup>: hypertension, diabetes, hypercholesterolemia, coronary artery disease, history of prior ischemic stroke. Prior use of antiplatelet drugs, antihypertensive drugs, and statins was assessed<sup>30</sup>. Laboratory measures prior to IVT/IAT included blood glucose levels, creatinine<sup>27</sup>, platelet count, international normalized ratio, activated Partial Thromboplastin Time (aPTT), and calibrated anti factor-Xa assays for rivaroxaban, if available and applicable. Current use of VKA or NOAC was recorded. In patients taking NOAC: agent and daily dosage, indication, last intake (in hours prior to IVT/IAT), and categorized reason for using IVT/IAT treatment were recorded. Functional outcome was assessed by outpatient visits or telephone interviews using the modified Rankin Scale (mRS) at 3 months.

### **Outcome measures**

Primary outcome measures were defined as the occurrence of ICH in three categories, or death within 3 months (i.e., mRS of 6, denoted as mRS<sub>6</sub>). ICH included: (i) any ICH on follow-up imaging including hemorrhagic transformation (ICH<sub>any</sub>); (ii) symptomatic ICH according to the criteria of the ECASS-II trial<sup>31</sup> (sICH<sub>ECASS-II</sub>); and (iii) sICH based on the criteria of the NINDS thrombolysis trial<sup>32</sup> (sICH<sub>NINDS</sub>).

Secondary outcome measures were: (i) NIHSS after 24 hours; (ii) major neurological improvement within 24 hours, defined as an improvement in NIHSS score of 8 points at 24 hours compared to initial NIHSS (or an NIHSS score of 0 at 24 hours) as defined in prior research<sup>33</sup>; and (iii) favorable 3-month outcome (i.e., mRS of 0, 1, or 2, denoted as mRS<sub>0-2</sub>).

### **Subgroup analyses**

First, patients treated with IVT only (i.e., excluding those with IAT only) were analysed by comparing all groups. Second, in NOAC patients, all patients with IVT/IAT decisions based on the findings of the calibrated anti factor-Xa assays were descriptively analysed. Third, post-hoc, we compared NOAC patients with VKA patients stratified to the INR in 2 strata: VKA with INR >1.7 and those with INR ≤1.7.

## Statistical analyses

Propensity score matching was used for analyses. Due to the heterogeneous sample sizes between groups, we used triple group (TriMatch<sup>34</sup>) propensity score matching (PSM<sup>35</sup>) to balance characteristics of patients according to baseline covariates. Variables likely to affect outcome or complications were chosen based on previous studies<sup>27-30</sup>. The variables included as predictors in PSM were age, sex, time-to-treatment, admission NIHSS, systolic and diastolic blood pressure, blood glucose level, creatinine as well as prior medication with statins, antihypertensive agents or antiplatelets, and the presence of diabetes, hypertension, hypercholesterolemia, coronary artery disease, atrial fibrillation, and history of prior ischemic stroke.

We employed a bootstrapping procedure<sup>36</sup> that combined propensity score matching with multiple imputation<sup>37</sup>. Patients in the NOAC groups, VKA and no-oAC, and groups were then matched based on their propensity scores<sup>38</sup>. Subsequent statistical analyses were carried out on the matched samples. The procedure was repeated 50.000 times to gain a reliable bootstrap estimation of the empirical distribution of test statistics and *p*-values.

Overall differences in NIHSS at 24 hours were analysed with univariate analysis of variance (ANOVA) with treatment group as the between subjects factor. Pairwise comparisons between treatment groups were computed as a-priori contrasts. Overall differences in the proportion of patients with ICH<sub>any</sub>, major neurological improvement, mRS<sub>0-2</sub>, and mRS<sub>6</sub> were tested with  $\chi^2$  tests. Pairwise differences between treatment groups for ICH<sub>any</sub>, major neurological improvement, mRS<sub>0-2</sub>, and mRS<sub>6</sub> were assessed with 2-sample binomial tests. Pairwise differences for sICH<sub>NINDS</sub> and sICH<sub>ECASS-II</sub> were tested using Fisher's exact test. Overall differences for sICH<sub>ECASS-II</sub> and sICH<sub>NINDS</sub> could not be evaluated due to very low incident rates in the NOAC group. Only pairwise Fisher's exact tests were computed. Odds ratios (OR) and their 95% confidence intervals are provided for all instances of statistical significance.

In a post-hoc analysis, three subgroups of patients were defined: patients on VKA with INR >1.7 (VKA<sub>INR>1.7</sub>), patients on VKA with INR ≤1.7 (VKA<sub>INR≤1.7</sub>) and patients on NOAC. We conducted the same set of statistical tests as described before. Due to tolerable differences in sample sizes between the three groups, no propensity score matching was required.

Statistical analyses were performed using R for Windows, version 3.1.2. All tests were 2-tailed, and statistical significance was determined at  $\alpha$  level of 0.05. For pairwise tests between groups,  $\alpha$  was corrected for multiple comparisons using the Šidák correction<sup>39</sup>.

**Ethics:** The study was approved by the ethics committee in Basel Switzerland. The requirement for additional local ethical approval differed among participating centers and was acquired as necessary.

## Results

### Study population

Our NOAC cohort comprised of 78 patients (apixaban  $n=2$ , dabigatran  $n=29$  and rivaroxaban  $n=47$ ). IVT was used in 51 NOAC patients, including 6 who received IVT followed by IAT. IAT only was used in 27 NOAC patients, in 25/27 patients with purely mechanical thrombectomy. The comparison groups comprised of (i) 441 VKA patients and (ii) 8938 no-NOAC patients (online supplemental Table 1).

### Baseline characteristics

There were significant differences in baseline characteristics between all cohorts. Baseline characteristics and recanalization therapies applied are displayed in Table 1.

### Last intake, coagulation parameters and indication for NOAC treatment

For NOAC patients, the median time between last intake and IVT/IAT was 13 hours (IQR 8-22h); it was <12 hours in 38 patients, 13-24 hours in 30 patients, 25-48 hours in 7 patients; and unknown (but still within <48 hours) in 3 patients. Atrial fibrillation was the indication for the NOAC use in 69 of 78 (88%) patients. Other indications included prevention ( $n=2$ ) and treatment ( $n=3$ ) of deep vein thrombosis and other/ not recorded ( $n=4$ ).

In patients receiving rivaroxaban ( $n=47$ ), the median INR was 1.3 (IQR 1.1-1.51) and the mean aPTT was 32 seconds (IQR 27-35 seconds); in patients receiving dabigatran ( $n=29$ ), median INR was 1.3 (IQR 1.1-1.5) and mean aPTT 32 seconds (IQR 27-35 seconds). The 2 patients under apixaban had an INR of 1.18 and 1.16 and an aPTT of 32 and 33 seconds, respectively.

In the VKA-group, the median INR was 1.3 (IQR 1.1–1.58). In 308 VKA patients (69.8%), the INR was  $\leq 1.7$ . In 80 VKA patients (18.1%) no INR was recorded. Among the 53 VKA-

patients (12%) with INR >1.7 (INR median 2.0; IQR 1.9-2.35), 37 were treated with IVT, while 16 had IAT (INR median 2.15, IQR 2.0-2.87).

The decision to use IVT/IAT in NOAC patients was based on the reported time since last intake >24 hours ( $n=10$ ), low concentrations levels in drug-specific coagulation assays ( $n=23$ ), on normal values in routine coagulation assays ( $n=10$ ), or on other/or unknown reasons ( $n=35$ ). The latter included patients, in which the use of NOAC was neither known nor suspected prior to IVT/AT treatment but was discovered thereafter.

## Outcome measures

*Primary outcome measures:* ICH<sub>any</sub> was observed in 14 of 76 (18.4%) NOAC patients compared to 105 of 394 (26.6%) on VKA patients, and 1332 of 7677 (17.4%) patients in the no-oAC group. ( $p = .304$ ). sICH<sub>ECASS-II</sub> occurred in 2 of 76 (2.6%) NOAC-patients compared to 27 of 415 (6.5%) VKA-patients and 417 of 8281 (5.0%) no-oAC patients ( $p = .484$ ). sICH<sub>NINDS</sub> was reported for 3 of 76 (3.9%) NOAC-patients, c, 40 of 432 (9.3%) VKA-patients and 616 of 8539 (7.2%) no-oAC patients ( $p = .560$ ). At 3 months, 17 of 74 (23.0%) NOAC-patients had died compared to 113 of 420 (26.9%) VKA-patients and 1172 of 8414 (13.9%) no-oAC patients ( $p = .438$ ) (Table 2).

*Secondary outcome measures:* A favorable 3-month outcome had 30 of 74 (40.5%) NOAC-patients compared to 166 of 420 (39.5%) VKA-patients and 4736 of 8414 (56.3%) no-oAC patients. Here, we find the only significant overall difference of frequencies in our data ( $p = .037$ ). The pattern of frequencies suggests a more favorable 3-month outcome for no-oAC patients than for the VKA and the NOAC-patients. Pairwise comparisons, however, remain insignificant in all cases (all  $p > .05$ ). Major neurological improvement occurred similarly often in all three groups (Table 2)

## Subgroup analyses

### *IVT only:*

IVT only was used in 51 NOAC and 390 VKA patients. ICH<sub>any</sub> occurred in 8 (15.7%) patients on NOAC and 54 (28.7%) patients on VKA.. sICH<sub>ECASS-II</sub> and sICH<sub>NINDS</sub> occurred in 2 (4.0%) patients on NOAC each, compared to 7 (3.6%) and 11 (5.7%) patients on VKA.

#### *IVT/IAT and calibrated anti factor-Xa assays*

In 21 taking rivaroxaban), decision to administer IVT was based on calibrated anti factor Xa-assays with a mean level of 21ng/ml (IQR 8-23ng/ml). In all patients on rivaroxaban receiving IVT measured anti factor Xa-levels were below 100ng/ml. Each of those 3 patients with a measured anti factor Xa-levels of > 100ng/ml (range 146-246ng/ml) had IAT only. None had sICH.

#### *NOAC and VKA $_{INR>1.7}$ or VKA $_{INR\leq 1.7}$*

Primary and secondary outcome measures for the subgroup analysis comparing patients on NOAC and VKA  $_{INR>1.7}$  or VKA  $_{INR\leq 1.7}$  are summarized in table 3. Pairwise Fisher's Exact Tests reveals a significant pairwise difference for sICH<sub>ECASS-II</sub> only between VKA  $_{INR>1.7}$  ( $n=16$ , 11.9%) and VKA  $_{INR\leq 1.7}$  ( $n=24$ , 8.1%, OR = 2.751; [1.963, 3.539]) but not for any other outcome measure or between other groups.

## **Discussion**

This observational multicenter pilot study yielded the following key findings: first, in selected patients with acute ischemic stroke who are on current NOAC treatment (last intake <148 hours), IVT/IAT was feasible and not associated with an excessive risk of ICH compared to patients on VKA or without oral anticoagulation. Second, compared to VKA patients NOAC patients had – numerically - fewer intracranial hemorrhages, lower death rates, and a better functional outcome. However, none of these differences reached statistical significance.

Overall, our study highlights that – at least in experienced stroke centers - IVT/IAT application in carefully selected acute ischemic stroke patients under NOAC treatment did not raise any suggestion of safety concerns.

The percentage of sICH<sub>ECASS-II</sub> (2.6%) or sICH<sub>NINDS</sub> (3.9%) in our NOAC cohort was comparable to sICH rates in a recent multicenter analysis (i.e. 4.7%)<sup>40</sup> and in the ECASS-3 study (5.3%)<sup>41</sup>. However, this finding might not be necessarily reassuring, as the upper limit of the 95%CI (i.e. 6.13% for sICH<sub>ECASS-II</sub> and 8.2% for ICH<sub>NINDS</sub>, respectively) indicates that the sICH risk might still be higher than that of reported data. Nevertheless, based on the observation that the ICH risk in all categories was numerically lower in NOAC than in VKA patients, this scenario seems unlikely, especially taking into account that IVT/IAT in VKA patients has generally been reported to be safe<sup>8,9</sup>. Reasons for this relative safety of IVT/IAT

under NOAC may include the lower baseline risk of ICH of such drugs, including in stroke patients<sup>3</sup>.

In approximately 25% of the NOAC treated patients, the decision to use IVT/IAT was based on rivaroxaban concentration levels in the calibrated anti factor Xa-assay. The same approach has also been utilized in two recent case reports<sup>19, 21</sup>. All these patients treated with IVT (i.e., from the mentioned case reports and our cohort) had levels of the calibrated anti factor Xa-assay <100ng/ml. None of these altogether 24 patients had sICH and only 1 had an asymptomatic ICH. Thus this threshold, recommended previously based on purely theoretical and pharmacological considerations and data<sup>11</sup>, may indeed serve as a clinically useful tool to select patients. However, given the small sample size our results should be interpreted with caution. Thus, further research about the clinical meaning of NOAC concentration thresholds is still needed.

Our analysis had the following strengths: (i) We report on a multicenter cohort rather than on a single or several cases of acute ischemic stroke while under treatment with NOAC; (ii) data ascertainment was undertaken systematically and included two comparison groups (i.e., VKA patients and patients without prior anticoagulation with IVT/IAT); and (iii) safety issues as well as functional outcome at 3 months were addressed.

Nevertheless, several potential limitations should be noted: First, this is a retrospective study. Second, there was heterogeneity between centers with regard to the criteria applied for the decision to use or avoid IVT/IAT in individual patients, and whether IVT or IAT was preferred. Third, NOAC patients differed from the VKA- and the no-oAC-patients in several baseline characteristics. Despite application of propensity score matching as an effort to minimize confounding effects, we cannot rule out the possibility that unmeasured characteristics might have differed between these patients and confounded our results. Fourth, we do not have a comparison group of patients on NOAC and acute ischemic stroke not treated with IVT/ IAT, so the bleeding risk in acute ischemic stroke patients under NOAC treated with IVT/IAT versus those without IVT/IAT could not be studied. Fifth, despite being the largest cohort available so far, the total numbers of patients taking NOAC or VKA are still relatively small. Thus, subgroup analyses, including patients with results of drug specific coagulation assays were limited. Therefore, we stress the pilot character of our study and urge to a cautious interpretation of our findings.

While safety of IVT in patients on VKA and an INR less or equal to 1.7 has been established based on large cohorts<sup>8, 9</sup>, knowledge about NOAC is extremely limited in comparison. The use of IVT in patients under NOAC has been reported only in single cases so far showing feasibility<sup>14-18, 20, 21, 24</sup>. Data from animal models showed no excessive risk of ICH after IVT in rodents with a prior treatment with rivaroxaban<sup>42, 43</sup>, dabigatran<sup>44, 45</sup>, and apixaban<sup>43</sup> compared with VKA. Currently, the use of IVT for acute ischemic stroke in patients with a recent (<48 hours) intake of a NOAC is regarded off-label<sup>7</sup>. Indeed, a recent survey among US vascular neurologists showed a remarkable lack of consensus regarding the management of patients with acute ischemic stroke that were taking dabigatran.<sup>46</sup> The guidelines of the American Heart Association/American Stroke Association state that IVT might be considered "[if] sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function)<sup>7</sup>. Nevertheless, NOAC have only limited influence on standard coagulation assays<sup>47</sup>. Practical approaches for the use of IVT and IAT in stroke patients on NOAC have been proposed<sup>10, 11</sup>. A recently developed and prospectively assessed approach for patients on dabigatran using aPTT and thrombin time in a US study reported 2 patients receiving IVT within 8 month of recruitment with no sign of ICH in these patients {Kate, 2014 #101}. No larger prospective study has yet evaluated the proposed thresholds.

Twenty-seven of our NOAC patients were treated with IAT only; 25 of those with pure mechanical thrombectomy. sICH was absent in all patients and also in the only case report of mechanical thrombectomy in NOAC patient with acute stroke we are aware of<sup>24</sup>. Although these numbers were small, the absence of sICH might suggest, that in patients with abnormal hemostasis and NOAC-treatment, mechanical recanalization strategies might be more appropriate. However, it remains to be shown, whether sICH rates are indeed lower when NOAC-patients with acute stroke are treated with pure mechanical IAT than with IVT. For patients with abnormal hemostasis<sup>48, 49</sup> and treatment with IAT, sICH rates were 7.1%<sup>48</sup> and 11.4%<sup>49</sup> which were numerically higher than those observed in our NOAC cohort treated with IVT.

In conclusion, our data suggest that IVT/IAT treatment in patients who have an acute ischemic stroke despite NOAC is feasible and probably not associated with an excessive risk for ICH. However, this assumption requires that patients (i) are treated in experienced stroke

centers and (ii) are carefully selected based on time from last intake of the oral anticoagulant and/or the findings of specific coagulation tests. Nevertheless, our observations must be considered with caution prior to generalizing them to standard practice. More research is needed, which should include a systematic assessment of the clinical meaning of coagulation tests and drug doses with regard to safety and effectiveness measures. **With these considerations in mind, we set up a prospective multi-center registry to systematically investigate the management of patients with acute ischemic stroke while taking novel oral anticoagulants (NOACISP ACUTE, Clinicaltrials.gov: NCT02353585).**

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#### Appendix:

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Disclosure:

DJS, RJH, CHN, YB, GT, BI, EB, MP, NDP, DS, WP, AZ, AT, LT, RS, AL, CT, NP, PHL, AC, DJW, HE, JB none.

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TT: Research contracts with Boehringer-Ingelheim, H. Lundbeck A/S, and Bayer. Advisory board memberships: Boehringer-Ingelheim, H. Lundbeck A/S, Bayer, and Bayer.

LHB has received funding from the Swiss National Science Foundation, the University of Basel, and the Swiss Heart Foundation, received travel honoraria from Bayer and served on scientific advisory boards for Bayer.

PAL has served on scientific advisory boards for Bayer Schering Pharma, Boehringer Ingelheim and BMS/Pfizer; has received funding for travel or speaker honoraria from Bayer Schering Pharma, Boehringer Ingelheim, and Shire plc; y; and has received research support from AstraZeneca, Boehringer Ingelheim, Sanofi-aventis, Photo-Thera, the Science Funds [Wissenschaftsfonds] of the University Hospital Basel, Swiss National Science Foundation, and the Swiss Heart Foundation.

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**Table 1 Baseline characteristics of patients who had recanalization therapies while under treatment with a NOAC, a VKA or no-oAC.**

	Novel oral anticoagulants (n = 78)	Vitamin K antagonists (n = 441)	no-oAC (n = 8938)	Statistics
Age in years, median (IQR)	76 (68-81)	77 (68-83)	71 (60-79)	p < .001 <sup>a</sup>
Female gender, n (%)	36 (49.3%)	201 (45.6%)	3915 (43.9%)	p = .495 <sup>b</sup>
Time-to-treatment time in minutes, median (IQR)	174.5 (115.5-240)	140 (90-185)	126 (80-175)	p < .001 <sup>a</sup>
Baseline NIHSS score, median (IQR)	14.5 (7-19)	14 (8-19)	10 (6-16)	p < .001 <sup>a</sup>
INR, median (IQR)	1.14 (1.06-1.3)	1.3 (1.1-1.6)	1 (1-1.1)	p < .001 <sup>a</sup>
Occlusion of intracranial artery, n (%)	50 (75.8%)	174 (68.5%)	2070 (46.7%)	p < .001 <sup>b</sup>
Systolic blood pressure in mm Hg, mean (IQR)	148 (127.5-164.5)	151.5 (132-170)	154 (139-170)	p = .148 <sup>a</sup>
Diastolic blood pressure in mm Hg, mean (IQR)	80 (67-93.5)	83 (73-94)	83 (74-94)	p = .175 <sup>a</sup>
<b><i>Type of acute recanalization therapy</i></b>				
IV thrombolysis only, n (%)	45 (57.7%)	354 (84.9%)	7788 (93.2%)	p = n.a. <sup>c</sup>
IV thrombolysis and IA treatment, n (%)	6 (7.69%)	36 (8.63%)	521 (6.24%)	
IA treatment only, n (%)	27 (34.62%)	27 (6.47%)	43 (0.51%)	
<b><i>Concomitant treatment</i></b>				
Prior use of statins, n (%)	27 (39.1%)	160 (38%)	1954 (25.5%)	p < .001 <sup>b</sup>
Prior use of antihypertensive drugs, n (%)	61 (87.1%)	346 (82.2%)	4424 (54.4%)	p < .001 <sup>b</sup>
Prior treatment with antiplatelets, n (%))	14 (18.2%)	64 (14.8%)	3008 (35.8%)	p < .001 <sup>b</sup>
<b><i>Risk factors</i></b>				
Atrial fibrillation, n (%)	68 (87.2%)	345 (78.8%)	2152 (24.3%)	p < .001 <sup>b</sup>
Diabetes mellitus, n (%)	17 (24.3%)	98 (22.2%)	1500 (16.8%)	p = .066 <sup>b</sup>
Hypertension, n (%)	61 (87.1%)	349 (79.1%)	5627 (63.2%)	p < .001 <sup>b</sup>
Hypercholesterolemia, n (%)	32 (49.2%)	184 (42.5%)	3559 (41.4%)	p = .450 <sup>b</sup>
Coronary artery disease, n (%)	24 (34.3%)	107 (25.4%)	1371 (16.9%)	p < .001 <sup>b</sup>
Prior history of stroke, n (%)	18 (25.4%)	110 (25.4%)	1211 (14%)	p < .001 <sup>b</sup>
<b><i>Stroke Etiology (TOAST criteria)</i></b>				
Cardioembolic, n (%)	64 (85.3%)	224 (61.4%)	2623 (33.1%)	p = n.a. <sup>c</sup>
Large artery atherosclerosis, n (%)	2 (2.7%)	97 (26.6%)	2003 (25.3%)	
Small artery occlusion, n (%)	0 (0%)	3 (0.82%)	574 (7.25%)	
Other, n (%)	1 (1.33%)	11 (3.01%)	338 (4.27%)	
More than 1 or undetermined, n (%)	8 (10.67%)	29 (7.95%)	2233 (28.21%)	

Note: <sup>a</sup> Kruskal-Wallis test with  $df = 2$

<sup>b</sup>  $\chi^2$ -test with  $df = 2$

<sup>c</sup> No test computed due to low sample sizes in one or more subgroups

**Table 2: Primary and secondary outcome measures:**

	Novel oral anticoagulants (n = 78)	Vitamin K antagonists (n = 441)	no-oAC (n = 8938)
<b>Primary outcome</b>			
ICH <sub>any</sub>	14 of 76 (18.4%)	105 of 394 (26.6%)	1332 of 7677 (17.4%)
sICH <sub>ECASS-II</sub>	2 of 76 (2.6%)	27 of 415 (6.5%)	417 of 8281 (5.0%)
sICH <sub>NINDS</sub>	3 of 76 (3.9%)	40 of 432 (9.3%)	616 of 8539 (7.2%)
Death at 3 months (mRS <sub>6</sub> )	17 of 74 (23.0%)	113 of 420 (26.9%)	1172 of 8414 (13.9%)
<b>Secondary outcome</b>			
NIHSS at 24 hours, median (IQR)	9 (2-14)	8 (3-16)	5 (2-13)
Major neurologic improvement	24 of 77 (31.2%)	128 of 405 (31.6%)	1958 of 6834 (28.7%)
Favorable clinical outcome at 3 months (mRS <sub>0-2</sub> )	30 of 74 (40.5%)	166 of 420 (39.5%)	4736 of 8414 (56.3%)

**Definitions:**

ICH<sub>any</sub> – any hemorrhage seen on follow-up imaging

sICH<sub>ECASS-II</sub> – any hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by  $\geq 4$  points than the value at baseline or the lowest value in the first 7 days, or any hemorrhage leading to death.

sICH<sub>NINDS</sub> – any hemorrhage on follow-up imaging and any decline in neurological status

Major neurologic improvement – improvement in NIHSS score of 8 points at 24 hours compared to initial NIHSS (or NIHSS score of 0 at 24 hours)

**Table 3: Outcome measures stratified to VKA with INR subgroups versus NOAC patients:**

	Vitamin K antagonists		Novel oral anticoagulants (n = 78)
	INR >1.7 (n = 135)	INR ≤1.7 (n = 306)	
<b>Primary outcome</b>			
ICH <sub>any</sub>	36 of 123 (29.27%)	69 of 271 (25.46%)	14 of 76 (18.42%)
sICH <sub>ECASS-II</sub>	13 of 116 (11.21%)	14 of 299 (4.68%)	2 of 76 (2.63%)
sICH <sub>NINDS</sub>	16 of 135 (11.85%)	24 of 297 (8.08%)	3 of 76 (3.95%)
Death at 3 months (mRS <sub>6</sub> )	38 of 129 (29.46%)	75 of 291 (25.77%)	17 of 74 (22.97%)
<b>Secondary outcome</b>			
NIHSS at 24 hours, median (IQR)	9 (3-17)	8 (3-16)	9 (2-14)
Major neurologic improvement	42 of 123 (34.15%)	86 of 282 (30.50%)	24 of 77 (31.17%)
Favourable clinical outcome at 3 months (mRS <sub>0-2</sub> )	57 of 129 (44.19%)	109 of 291 (37.46%)	30 of 74 (40.54%)

Note: Definitions as in Table 2.

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